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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,563	04/15/2004	Henriette Gourdeau	PHARMA 100 D2	6418

24999 7590 10/02/2006

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,563	GOURDEAU ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-50* is/are pending in the application.

4a) Of the above claim(s) *22,27-33,36 and 38-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-21,23-26,34,35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 11-50 are currently pending. Claims 22, 27-33, 36 and 38-50 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 11-21, 23-26, 34, 35 and 37 are under exam and are the subject of this Office Action. This is the first Office Action on the merits of the application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 11-26 and 34-37 in the reply filed on 9/5/2006 is acknowledged. The traversal is on the ground(s) that to search the composition claims along with the method claims would not be an undue burden. This is not found persuasive because the compositions and methods are distinct and would require separate searches for the reasons set forth in the restriction requirement mailed 6/2/2006. The requirement is still deemed proper and is therefore made **FINAL**.

Applicant's election of the species (-)-β-L-dioxolane-cytadine and the biological modifier filgrastim without traverse in the reply filed on 9/5/2006 is acknowledged. In response to applicant's request for clarification on why an election of a single biological response modifier (Claim 18) was required, examiner respectfully submits that the modifiers recited in claim 18 are structurally distinct and would require different searches. For example, a search for rituxan (an antibody) would not result in prior art drawn to epoetin (a glycoprotein hormone) and *vice versa*.

Claims 22, 27-33, 36 and 38-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/5/2006.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. § 119(e) or under 35 U.S.C. § 120, 121, or 365(c) is acknowledged. The earliest effective U.S. filing date of the instant application has been determined to be March 29, 1999.

Information Disclosure Statement

Acknowledgement is made of receipt of the information disclosure statements (IDS) filed 6/1/2004 and 6/17/2004. The information contained therein has been reviewed by the examiner to the extent that each is a proper prior art citation.

Specification

The disclosure is objected to because of the following informalities: page 12 appears to be missing text, as it is mostly blank (only two lines of text). Appropriate correction is required.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 16 and 17 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, claim 14 recites "multidrug resistance reversing agent[s]" and "biological response modifiers." Dependent claim 16 limits the biological response modifiers to "monoclonal antibodies" and "cytokines". Claim 17 limits cytokines to "interferons, interleukins and colony-stimulating factors." There is insufficient written description in the disclosure for the following genus:

1) Multidrug resistance reversing agents

2) Biological response modifiers

The specification only describes ONE multidrug resistance reversing agent, PSC 833 (page 16). There is no description of any structural features, methods of synthesizing, isolating or testing for any other multidrug resistance reversing agents.

"Biological response modifiers" are only described in the specification as monoclonal antibodies or cytokines (page 16) and only a limited number are sufficiently described (page 17 and Claim 18). Only the specifically named biological response modifiers satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one

must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

While the specification describes one specie of multidrug resistance reversing agent (PSC 833) (page 16; Claim 15) and a few species of the instantly claimed biological response modifiers at page 17 and in Claim 18, it does not describe a sufficient number of species as to convey possession of the entire genus encompassed by "multidrug resistance reversing agent" and "biological response modifier." Applicants have provided no direction on how one would test whether an agent is a "biological response modifier" or a "multidrug resistance reversing agent" nor have they sufficiently described structural features necessary to retain biological activity. As such, only the specifically named agents (*e.g.* PSC 833, rituxan, filgrastim, etc.) are sufficiently described so as to allow one skilled in the art to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 11-14, 16-17, 19-21, 23-26, 34, 35 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/07413 (prior art of record), hereinafter "WO".

The instant claims are drawn to a method of treating leukemia by administering a combination of cytarabine and (-)-β-L-dioxalane-cytadine (β-L-OddC).

WO discloses the use of (-)-(*2S,4S*)-L-(2-hydroxymethyl-1,3-dioxolan-4-yl)cytosine (also referred to as (-)-OddC, L-OddC, or (-)-L-OddC) in the treatment of cancer (page 5, lines 17-27; page 47, Claim 12). The compound is administered as its substantially "-" enantiomer (*i.e.* free of the "+" enantiomer) (page 6, lines 6-11). WO defines "enantiomerically enriched" to refer to a nucleoside composition that includes at least approximately 95%, and preferably approximately 97%, 98%, 99%, or 100% of a single enantiomer of that nucleoside. In a preferred embodiment, (-)-L-OddC or its derivative or salt is provided in a nucleoside composition that consists essentially of one enantiomer, *i.e.*, as the indicated enantiomer (the L-enantiomer) and substantially in the absence of its corresponding D-enantiomer (*i.e.*, in enantiomerically enriched, including enantiomerically pure form) (page 11, lines 6-18).

Leukemia is recited as one type of cancer (-)-L-OddC can be used to treat (page 6, lines 22-28). It is further disclosed that (-)-L-OddC can be administered in combination with other

anticancer agents, including interferons, interleukins and cytarabine (page 7, line 21 to page 8, line 20). Figure 3 shows the results of treatment of P388 (an experimental lymphocytic leukemia cell line) leukemic mice with (-)-L-OddC. Further, the *in vitro* activity of (-)-L-OddC was demonstrated against several different leukemia cell lines (Table 2, page 35).[1] These tested leukemia cell lines correspond to an acute lymphoblastic cell line (CCRF-CEM), an acute promyelocytic leukemia cell line (HL-60), a chronic myelogenous leukemia (CML) cell line (K-562) and an acute lymphoblastic leukemia cell line (MOLT-4).

Cytarabine is disclosed to be a useful agent in the treatment of acute myeloid leukemia and is also active against acute lymphocytic leukemia, and to a lesser extent, chronic myelocytic leukemia and non-Hodgkin's lymphoma (page 37, lines 23-33). The *in vitro* cytotoxic activity of cytarabine and (-)-L-OddC was compared against several cell lines, including an acute lymphoblastic cell line (CEM) (page 40). (-)-L-OddC was more potent than cytarabine against this leukemia cell line.

Thus, WO discloses the treatment of cancer, including leukemias, with the instantly claimed compound. It is further disclosed that (-)-L-OddC can be administered with other agents, including the instantly claimed cytarabine, interferons and interleukins. (-)-L-OddC is provided in substantially the "-" enantiomer and has demonstrated efficacy in the treatment of leukemia. WO further discloses that cytarabine is a known agent used in the treatment of different leukemias, including acute myeloid leukemia, acute lymphocytic leukemia, and to a lesser extent, chronic myelocytic leukemia.

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[1] It is noted that the leukemia cell lines in Table 2 are not properly identified. It is believed that RL-60(TB) is HL-60; BSOLT-4 is MOLT-4; and RPMI-2.26 is RPMI-82.26.

Given the above disclosure, it would have been *prima facie* obvious at the time the invention was made to combine (-)-L-OddC and cytarabine in a method to treat leukemia. The skilled artisan would have been motivated to do so given the disclosure of the WO reference which teaches the effectiveness of (-)-L-OddC in the treatment of leukemia cell lines and further suggests combining (-)-L-OddC with other agents to treat cancer. One skilled in the art would be further motivated to combine the two drugs in a single therapy given the known use of cytarabine in the treatment of leukemia. (-)-L-OddC and cytarabine are individually known in the art as agents for treating leukemia, whose efficacy when administered alone is well established for the treatment of a large number of different leukemias. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed supra). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Claims 11-21, 23-26, 34, 35 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/07413 as applied to claims 11-14, 16-17, 19-21, 23-26, 34-35 and 37

above, and further in view of Advani *et al.* (Blood, 1999, vol. 93, no. 3, February 1, pages 787-795) and Jamkubowski *et al.* (Leukemia, 1995, vol. 9, pages 1799-1804).

WO discloses as discussed *supra*. The reference does not disclose the administration of a combination of (-)-L-OddC and cytarabine further comprising PSC 833 or filgrastim in the treatment of leukemia. The Advani and Jamkubowski references specifically apply to the claim limitations of claims 15 and 18, respectively.

Advani *et al.* disclose that a potential mechanism of chemotherapy resistance in acute myeloid leukemia (AML) is the multidrug resistance (*MDR-1*) gene product P-glycoprotein (P-gp). It is further disclosed that PSC 833 (PSC) has been used clinically in preliminary studies for treating poor-risk AML (page 787, left column). PSC, a potent inhibitor of P-gp, demonstrates low immunosuppression and renal toxicity (*id.*). The reference reports a phase II trial evaluating PSC in combination with mitoxantrone, etoposide and cytarabine in the treatment of AML patients with poor prognostic features.

Jamkubowski *et al.* disclose the treatment of patients with acute myelogenous leukemia with granulocyte colony-stimulating factor (filgrastim) (Abstract).

It would have been *prima facie* obvious at the time the invention was made to administer PSC 833 or filgrastim in a combination therapy to treat leukemia. WO discloses the treatment of leukemia with (-)-L-OddC and further suggests combining (-)-L-OddC with other anticancer agents. Advani *et al.* demonstrate that PSC can be combined with chemotherapeutics to overcome P-gp mediated drug resistance in AML patients. Jamkubowski *et al.* disclose the treatment AML patients with filgrastim.

As noted above, it is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Thus, because (-)-L-OddC, cytarabine, PSC 833 and filgrastim were all well known in the art as treatments for leukemia, it would have been *prima facie* obvious to combine one or more of them in a combination therapy to treat leukemia. The skilled artisan would be imbued with at least a reasonable expectation that such a combined therapy would be an effective treatment, as each individual agent is known to be effective in the treatment of leukemia, both alone and in combination.

The natural presumption that two or more individually known antileukemic agents would, when combined, provide a third composition also useful for treating leukemia flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Claims 11, 13, 19, 21, 35 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Phillips *et al.* (Blood, 1991, vol. 77, no. 7, pages 1429-1435) in view of Grove *et al.* (Cancer Research, 1995, vol. 55, pages 3008-3011).

The instant claims are drawn to the treatment of leukemia by administering cytarabine and a compound of Formula I. The elected compound from Formula I is (-)-β-L-dioxolane-cytidine.

Cytarabine is well known in the art as a treatment for leukemia, both alone and in combination with other chemotherapeutic agents. For example, Phillips *et al.* disclose the treatment of acute myelogenous leukemia with a combination of cytarabine and daunorubicin (Abstract; page 1429). The reference does not disclose combining cytarabine with (-)-β-L-OddC to treat leukemia.

However, Grove *et al.* disclose that L-(-)-dioxolane-cytadine is the first L-nucleoside ever shown to have anticancer activity (Abstract). The *in vitro* cytotoxicity of (-)-β-L-OddC was shown to be similar to cytarabine in the leukemic CFM cell line (Table 1, page 3009) and was also shown to be effective *in vivo* against HepG2 and DU-145 tumors (Figure 3, page 3010).

It would have been *prima facie* obvious at the time the invention was made to administer cytarabine and (-)-β-L-OddC in a combination therapy to treat leukemia. Phillips discloses the treatment of acute myelogenous leukemia with cytarabine and daunorubicin. Grove *et al.* demonstrate that (-)-β-L-OddC is a novel anticancer agent with efficacy against leukemia cells.

As noted above, it is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Thus, because (-)-L-OddC and cytarabine were both known in the art as treatments for leukemia, it would have been *prima facie* obvious to combine one or more of them in a combination therapy to treat leukemia. The motivation to do so can be found in Phillips *et al.* who demonstrate that cytarabine combination therapy is an effective treatment for leukemia.

The skilled artisan would be imbued with at least a reasonable expectation that such a combined therapy would be an effective treatment, as each individual agent is known to be effective in the treatment of leukemia, both alone and in combination.

The natural presumption that two or more individually known antileukemic agents would, when combined, provide a third composition also useful for treating leukemia flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-13, 21, 34, 35 and 37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24 and 26 of copending Application No. 10/853,241. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims both recite administration of the same compounds to treat leukemia. Although the instant claims do not recite a specific ratio of cytarabine to a compound of Formula I, they encompass the ratios specified in the claims of the '241 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
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September 20, 2006

9/23/06
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SUPERVISORY PATENT EXAMINER